Sample Size Determination in the Safety Evaluation of FVIII Products

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* The views expressed in this presentation are not necessarily of the U.S. Food and Drug Administration.

Factor VIII

- Major safety concern
  - Inhibitor formation
- Sample size determination
  - Safety evaluation: Inhibitor formation

Read My Lips

$$P[T_2 \leq t_2] = P[T_1 - c_1(S) \leq t_2]$$

$$= P[T_1 - (S^2/n)\,\chi^{-1}(\alpha,k-1,\lambda_0(S,\delta)) \leq t_2$$

$$= P[(n/\sigma^2)T_1 - (S^2/\sigma^2)\,\chi^{-1}(\alpha;k-1,\lambda_0(S,\delta))$$

$$\leq (n/\sigma^2)t_2]$$

$$= P[\chi(k-1,\lambda_0(S,\delta)) \leq$$

$$(n/\sigma^2)t_2+(S^2/\sigma^2)\chi^{-1}(\alpha;k-1,\lambda_0(S,\delta))]$$

A Big Question

How do we determine the sample size?

How do we determine the sample size?

Question for a Statistician

What sample size do I need?

n

- Study design?
- Study objective?

Study Design

- Studies to date have lacked concurrent controls
- Relied on the “historical data”
- Compare the inhibitor formation rate (proportions) of the test product with an upper acceptable limit

Study Objective

- Want to show that the inhibitor formation rate is low.
  - The true inhibitor formation rate of the test product < an upper acceptable limit
    - Not the observed inhibitor formation rate
    - Upper confidence limit < upper acceptable limit
- How low is low?
  - Upper acceptable limit = ???

Upper Acceptable Limit

- 1%? Too low - Impossible to show
- 30%? Too high - Clinically unacceptable
- Need to make a cut somewhere in between
- Where?
- If the study succeeds (i.e., upper confidence limit < upper acceptable limit), then the true inhibitor formation rate of the test product is most likely to be much lower than the upper acceptable limit.

Sample Size

- Sample size depends on
  - Upper acceptable limit: Smaller ⇒ Larger n
  - Confidence level: Higher ⇒ Larger n
  - Number of inhibitors that are allowed to be considered a success for the study: More ⇒ Larger n
- Rule of three
  - Simple and useful tool

Rule of Three

- For a large n (e.g., n ≥ 20), if no inhibitors are observed, then the one-sided 95% upper confidence limit ≅ 3/n
  - Does not apply if one or more inhibitors are observed
  - Works for 95% confidence level only
  - Works for large n, e.g., n ≥ 20

Example

- Upper acceptable limit: 10%
- Confidence level: 95%
- Rule of three: One-sided 95% upper confidence limit ≅ 3/n (no inhibitors are observed)
- Set 3/n = 10%, then n = 30
- More accurate: n = 29
- If one inhibitor is observed out of 29 subjects, then the study fails.

Sample Size (2)

Allowing no inhibitor		
Confidence level	Upper acceptable limit	
	5%	10%
95%	59	29
97.5%	72	36

Allowing one inhibitor		
Confidence level	Upper acceptable limit	
	5%	10%
95%	93	46
97.5%	109	54

1/29; One-sided 95% upper confidence limit = 15%

1/46; One-sided 95% upper confidence limit = 9.90%

1/45; One-sided 95% upper confidence limit = 10.10%

FDA's Current Thinking

- Analyses will be Intent-to-Treat
- The upper limit of the two-sided 95% confidence interval for the inhibitor formation rate < 6.8%
  - Same as one-sided 97.5% confidence level
  - Upper acceptable limit = 6.8%
- Why 6.8%?
  - Allow one inhibitor out of 80 subjects

Inhibitor Formation Rate: Considerations

- Inhibitor formation rate depends on
  - Population: PTP or PUP
  - Definition of inhibitor formation
    - Lowest unacceptable inhibitor level
  - Duration of exposure: Number of exposure days (at least 50 in clinical trial)
  - Assays for detecting inhibitor formation
  - Others?
    - Subjects for discussions

Upper Acceptable Limit: Considerations

- Depends on the inhibitor formation rate for the “historical data”
  - If the “Historical data” is 1% to 2%, then 6.8% may be too high
  - If the “Historical data” is 3% to 4%, then 6.8% may be reasonable
- Need to estimate the inhibitor formation rate for the “historical data”

Why 6.8%?

- Where does 6.8% come from?
- Data driven
  - The upper limit of the two-sided 95% confidence interval for the inhibitor formation rate for observing one inhibitor out of 80 subjects is 6.77%.
  - To “pass” the outcome of one inhibitor out of 80 subjects, upper acceptable limit = 6.8%.
- Back calculation

Summary

- Sample size
  - Confidence level
  - Upper acceptable limit
  - Number of inhibitors that are allowed
- Need to estimate the inhibitor formation rate for the “historical data” so that the upper acceptable limit can be determined.

Two Interesting Topics

- Statistical power depends on
  - Upper acceptable limit
  - Confidence level
  - Sample size
  - True inhibitor formation rate
- If the study fails (the upper confidence limit > the upper acceptable limit), can we enroll more subjects?

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